The Royal Society

The curse of the pharaoh hypothesis

Sylvain Gandon

Laboratoire d'Ecologie, CNRS-UMR 7625, Université Pierre et Marie Curie, Bâtiment A, 7ème étage, 7 quai Saint Bernard, case 237, 75252 Paris, Cedex 05, France (sylvain.gandon@snv.jussieu.fr)

The 'curse of the pharaoh' has been used as a metaphor for the hypothesis that higher parasite propagule survival selects for higher virulence. Indeed, the mysterious death of Lord Carnavon after entering the tomb of the Egyptian pharaoh Tutankhamen could potentially be explained by an infection with a highly virulent and very long-lived pathogen. In this paper, I investigate whether parasite virulence increases with high propagule survival. In this respect, I derive an analytic expression of the evolutionarily stable level of parasite virulence as a function of propagule survival rate when the host–parasite system has reached a stable ecological equilibrium. This result shows that, if multiple infection occurs, higher propagule survival generally increases parasite virulence. This effect is enhanced when parasite dispersal coevolves with parasite virulence. In a more general perspective, the model shows the importance of taking into account the combination of direct and indirect effects (which I call inclusive effects) of higher transmission ability on the evolution of parasite virulence. The recognition of these effects has several practical implications for virulence management.

Keywords: virulence; kin selection; propagule survival; dispersal; multiple infection

1. INTRODUCTION

Virulence is often considered as a by-product of the parasite host-exploitation strategy. High levels of exploitation increase parasite within-host reproduction and allow transmission to new hosts. However, an extreme exploitation strategy has a cost as it decreases the life expectancy of the host and, as a consequence, the chance to be transmitted. This simple trade-off predicts that parasites should evolve toward intermediate levels of virulence (Anderson & May 1979; Ewald 1983; van Baalen & Sabelis 1995*a*; Frank 1996). In this respect it has been suggested that high propagule survival rates could decrease the cost of an extreme exploitation strategy, because a parasite that can survive outside its host will enhance its chances of being transmitted. This verbal argument led to the intuitive prediction that high survival of free-living stages should increase parasite virulence (Ewald 1987, 1993, 1994). This hypothesis is also known as the 'curse of the pharaoh' hypothesis (Bonhoeffer *et al.* 1996) in reference to the mysterious death of Lord Carnavon after entering the tomb of the Egyptian pharaoh Tutankhamen (Corelli 1923). One possible explanation for this death is an infection by a highly virulent and very long-lived infectious disease that lied dormant in the tomb of Tutankhamen. Bonhoeffer *et al.* (1996) formalized the previous argument in order to test the validity of this prediction. They found that, when the host–parasite system reaches an epidemiological equilibrium, the evolutionarily stable (ES) parasite virulence is not affected by the survival rate of parasite propagules. ES parasite virulence increases with survival only when the host–parasite system is in disequilibrium and when the death rate of the propagules is high relative to that of infected hosts. Their results can be placed in a broader perspective. As pointed out by Frank (1996, p. 54), during an epidemic selection acts mainly through parasite 'birth' rate (i.e. infection of new hosts), whereas at equilibrium it mainly acts through parasite 'death' rate (i.e. death rate of the host or clearance). In the curse of the pharaoh hypothesis, propagule survival only affects the 'birth' rate of parasites and, in agreement with the general prediction of Frank, survival affects the evolution of virulence only during epidemics (Bonhoeffer *et al.* 1996).

However, this is only one part of the prediction. Frank (1996) also pointed out that in both equilibrium and epidemic cases, as predicted by several authors (Eshel 1977; Bremermann & Pickering 1983; Frank 1994, 1996; Nowak & May 1994; May & Nowak 1995; van Baalen & Sabelis 1995*a*), multiple infections decrease relatedness among parasites within infected hosts, increase within-host competition and select for higher levels of virulence (for empirical tests of this prediction see Herre (1993), Frank (1996), Ebert & Mangin (1997) and Taylor *et al.* (1998)).

In this paper, following the latter argument, I investigate the effects of propagule survival on the evolution of parasite virulence after relaxing a major assumption of the Bonhoeffer *et al.* (1996) model, that is the absence of multiple infections. In this case, survival acts on the evolution of virulence through its effect on the probability of multiple infection and, as a consequence, on the average level of relatedness among parasites that share infected hosts. Following Frank (1994), I use a simple kin-selection model to study this effect. This minimal approach allows the study of different cases depending on whether dispersal is a fixed parameter or an evolving trait that can be correlated with parasite virulence (Frank 1994).

Received 31 March 1998 *Accepted* 11 May 1998

2. HOST AND PARASITE LIFE CYCLES

First assume that the environment is filled with an infinite number of hosts. Each host has an intrinsic (i.e. independent of parasite virulence) death rate, α, and a very large fecundity so that every dead host is replaced immediately by a newly produced one. However, for the sake of simplicity, I will only consider the case where $\alpha=0$ (i.e. host mortality is only due to parasite virulence). The effect of the intrinsic host mortality will be treated elsewhere.

The model further assumes the following parasite life cycle: (i) each individual host is infected by a constant number, N, of haploid and asexual parasites; (ii) the average within-host relatedness among parasites is R and throughout the paper I will assume that individuals from different populations are unrelated; and (iii) parasites compete against each other for resources provided by the host. The level of parasite competitivity is measured by v. (iv) I also assume that intra-host competition has a deleterious effect on hosts as the parameter v measures the parasite-induced host mortality (i.e. parasite virulence). I will further assume that the death of an infected host induces the extinction of the whole parasite population before parasite dispersal. Therefore, the extinction rate of parasite populations, e, will be equal to the overall host mortality. Very generally, $e=1-(1-\alpha)(1-v)$ but, because I assume no intrinsic host mortality, this yields $e=v$. The assumptions (iii) and (iv) induce a trade-off between parasite virulence and parasite transmission. I further assume that: (v) generations are discrete and non-overlapping; (vi) after reproduction a proportion, d, of the offspring leave their host and try to reach another; (vii) these propagules pay a cost of dispersal and fail to infect a susceptible host with a probability, c_0 (in the following, c_0 will be called the basic cost of dispersal); and (viii) unsuccessful propagules have a probability, s, to survive until the next generation. If parasite propagules reach the next generation they have another chance to infect a host. Under these assumptions a propagule will effectively infect a host with a probability β (i.e. the transmission efficiency of the parasite):

$$\beta = (1-c_0)\sum_{t=0}^{\infty}(c_0 s)^t = \frac{1-c_0}{1-c_0 s}. \tag{1}$$

Note the difference with classical epidemiological models (Anderson & May 1979, 1991; van Baalen & Sabelis 1995*a*). Here, β is a probability of transmission and not a rate of transmission. It is worth defining an effective cost of dispersal, c, which is

$$c = 1-\beta = \frac{c_0(1-s)}{1-c_0 s}. \tag{2}$$

I assume (ix) that parasite dispersal is further described by its mode of dispersal, which is characterized by the probability ϕ of common origin of migrants (Whitlock & McCauley 1990; Gandon & Michalakis 1999). In particular, when $\phi=0$ all immigrant parasites come from different hosts. For example, it might be the case for an air-borne disease (i.e. island model of dispersal). At the other extreme, when $\phi=1$ all immigrant parasites come from a single infected host (i.e. propagule pool model of dispersal). This situation might be closer to a vector-borne type of transmission or to a sexually transmitted disease. Finally, I also assume (x) that the parasite fecundity is sufficiently large to allow the infection of each susceptible host. Therefore, after the parasite dispersal phase all hosts are infected. At equilibrium the host population reaches a stable age structure distribution (Olivieri *et al*. 1995):

$$F_t = e(1-e)^t, \tag{3}$$

where F_t is the frequency of hosts of age t.

3. PARASITE INCLUSIVE FITNESS

My aim is to derive the evolutionarily stable strategies (ESSs) for parasite virulence and dispersal. The derivation of ESSs requires an explicit formulation of fitness of an individual parasite, i. As first pointed out by Hamilton (1964), the inclusive fitness of this individual will depend not only on its own success but also on the success of its related neighbours. As a consequence, the explicit formulation of the inclusive fitness requires the incorporation of the effects of relatives and, therefore, the characterization of the group j of age t that interacts with the individual i. In this respect, the virulence and the dispersal rate of a parasite i that shares an infected host of age t with a group j of parasites are v_{ij}^t and d_{ij}^t, respectively. Similarly, the average virulence and dispersal rate of a group of parasites in a host of age t are v_j^t and d_j^t, respectively, and, finally, the average virulence and dispersal rate of the parasite as a whole are v and d, respectively. The fitness (i.e. the expected number of progeny) of a parasite i that shares an infected host of age t with a group j of parasites is

$$W(v_{ij}^t, v_j^t, d_{ij}^t, d_j^t) = W_{\text{within}} W_{\text{between}}, \tag{4}$$

where W_{within} describes the within-host competition that occurs before dispersal and W_{between} describes the success of parasite transmission. A simple way to formalize both components of parasite fitness is to write

$$W_{\text{within}} = v_{ij}^t / v_j^t, \tag{5}$$

$$W_{\text{between}} = W_1 + W_2, \tag{6}$$

where W_1 and W_2 are the expected number of progeny of the parasite via philopatry or dispersal, respectively. Philopatric individuals will compete against both philopatric and immigrant individuals, which yields

$$W_1 = \frac{(1-e_j^t)(1-d_{ij}^t)}{1-d_j^t+(1-e)\beta d}, \tag{7}$$

where e_j^t is the extinction rate of the group j of parasites that infect a host of age t:

$$e_j^t = v_j^t. \tag{8}$$

Concerning the expected number of progeny via dispersal, we can write

$$W_2 = W_{2a} + W_{2b}, \tag{9}$$

where W_{2a} and W_{2b} refer to the contribution to fitness through dispersed parasites that reach an already-infected host (with probability $(1-e)$) or a newly produced and non-infected host (with probability e), respectively. In already-infected hosts the immigrant parasites compete against other immigrants as well as with residents. This leads to

$$W_{2a} = d_{ij}^t(1-e_j^t)(1-c)\sum_{t'=1}^{\infty}\frac{F_{t'}}{1-d^{t'}+(1-e)\beta((1-\phi)d+\phi\, d_j^t)}, \tag{10}$$

where the summation in the right-hand side of equation (10) gives the probability that a disperser parasite competing in a randomly chosen, already-infected host, wins a spot where it can reproduce (t' is the age of the randomly chosen host).

In newly infected hosts, parasites compete only with other immigrants and, therefore,

$$W_{2b} = e\frac{(1-e_j^t)d_{ij}^t}{(1-e)((1-\phi)d+\phi\, d_j^t)}. \tag{11}$$

The fitness W of a randomly chosen parasite i in a group j of neighbours is

$$W = \sum_{t=0}^{\infty}(F_t\, W(v_{ij}^t, v_j^t, d_{ij}^t, d_j^t)). \tag{12}$$

Following Frank (1994), I will use this general expression for parasite fitness to study the evolution of parasite virulence and parasite dispersal in different subcases depending on whether virulence and dispersal are linked traits or not.

4. VIRULENCE AND DISPERSAL ARE NOT LINKED

(a) *Evolution of virulence*

When virulence and dispersal are not linked the ES virulence and dispersal can be derived independently. Let me first focus on the evolution of virulence when dispersal is assumed to be a passive trait (i.e. a fixed parameter). In this case I assume that $d_{ij}^t = d_j^t = d$. It is easy to show from equations (4)–(12) that the expression for parasite fitness now reduces to:

$$W = \sum_{t=0}^{\infty}F_t\frac{v_{ij}^t}{v_j^t}\frac{(1-v_j^t)}{(1-v)}. \tag{13}$$

Interestingly, W does not depend on the parasite dispersal rate. Following the approach of Taylor & Frank (1996), this expression of parasite fitness can be used to derive the ES parasite virulence. Let the phenotype of individual parasites be determined by their genic value, x. I then select a random allele at this locus, mutate that allele and its identical by descent copies and ask if this mutant allele will increase in frequency. A standard condition for x^* to be evolutionarily stable is

$$\left.\frac{\mathrm{d}W}{\mathrm{d}x}\right|_{x=x^*} = 0 \quad (\text{for } 0\leqslant x^*\leqslant 1). \tag{14}$$

The derivative of W is the rate of change of the inclusive fitness, ΔW^{IF}, with a deviant value x. Using the chain rule I obtain:

$$\Delta W^{\mathrm{IF}} = \frac{\mathrm{d}W}{\mathrm{d}v_{ij}^t} = \sum_{t=0}^{\infty}F_t\left[\frac{\partial W(v_{ij}^t, v_j^t)}{\partial v_{ij}^t} + \frac{\partial W(v_{ij}^t, v_j^t)}{\partial v_j^t}R_t\right], \tag{15}$$

where

$$R_t = \frac{\mathrm{d}v_j^t}{\mathrm{d}v_{ij}^t} = \frac{\mathrm{cov}(v_j^t, x)}{\mathrm{cov}(v_{ij}^t, x)}, \tag{16}$$

is the relatedness between two randomly chosen parasites in an infected host of age t (see Appendix A). If I further assume that the strategy adopted by the parasite does not vary with the age of the host (i.e. $v_{ij}^t = v_{ij}$ and $v_j^t = v_j$), I obtain:

$$\Delta W^{\mathrm{IF}} = \frac{\partial W(v_{ij}, v_j)}{\partial v_{ij}} + \frac{\partial W(v_{ij}, v_j)}{\partial v_j}\sum_{t=0}^{\infty}(F_t\, R_t). \tag{17}$$

It might appear surprising to neglect the variation among populations of different ages at the phenotypic level (i.e. $v_{ij}^t = v_{ij}$) but not at the genotypic level (R varies with t). This apparent discrepancy can be explained by the fact that one can neglect phenotypic variation as soon as this variation is assumed to be very small. However, variation on genetic structure with the age of populations cannot be neglected because the concept of relatedness does not depend on phenotypic *similarity* but on genetic *identity* by descent. However, note that it is the average within-host relatedness, R, that matters:

$$R = \sum_{t=0}^{\infty}(F_t\, R_t). \tag{18}$$

The ES virulence, v^*, can be derived by setting equation (17) to zero. It yields

$$v^* = 1 - R. \tag{19}$$

This expression was already found by Frank (1994) in a simpler model (i.e. in the absence of host mortality). It shows that lower relatedness leads to higher levels of within-host competition and, as a consequence, higher parasite virulence.

However, relatedness is not a fixed parameter but itself varies as a function of several parameters including virulence and dispersal (the full derivation of relatedness is given in Appendix A). Assuming that relatedness is a dynamical variable implies that the ES virulence will depend indirectly on many parameters (see figure 1). As already noted by Frank (1994), higher parasite population sizes, N, and lower basic costs of dispersal, c_0, decrease relatedness among parasites and, as a consequence, increase the ES level of virulence. In contrast, higher probability of common origin increases relatedness and decreases the ES parasite virulence. Similarly, as propagule survival and parasite dispersal affect relatedness, these parameters also affect parasite virulence. Figure 2 shows that, when c_0 and ϕ are both high, higher propagule survival and higher dispersal rates tend to increase the ES virulence. Again, these effects are due to the indirect effects (i.e. via relatedness) of both these parameters. Higher dispersal rates and higher propagule

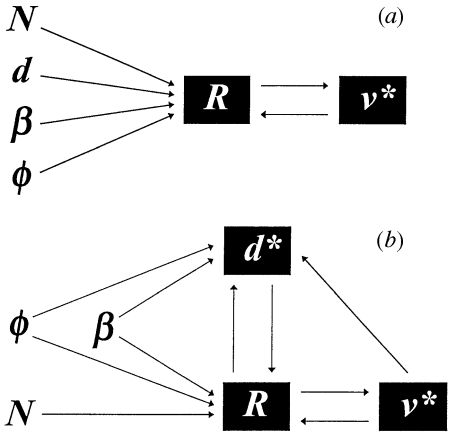

Figure 1. Indirect effects (via relatedness, R) of various parameters (N, s, β, ϕ) on the evolution of parasite virulence, v^*, when virulence and dispersal are unlinked traits. In (a) parasite dispersal, d, is a passive trait and in (b) dispersal, d^*, is coevolving with parasite virulence.

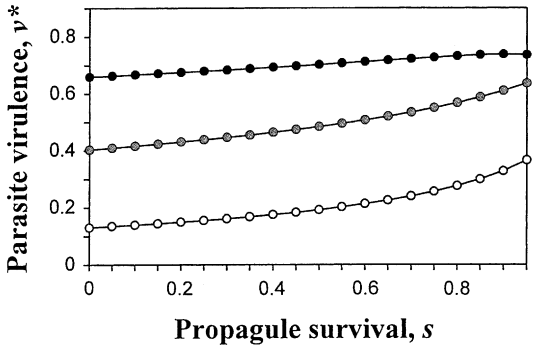

Figure 2. Evolution of virulence. Evolutionarily stable level of virulence, v^*, versus propagule survival rate, s, for three different parasite dispersal rates: $d=0.1$ (in white), $d=0.5$ (in grey), $d=0.9$ (in black). Other parameter values: $N=10$, $c_0=0.9$, $\phi=1$.

survival tend to increase the probability to harbour multiple infections. As a consequence, relatedness among parasites within infected hosts decreases and higher parasite virulence is selected for.

However, when c_0 and ϕ are low, the effect of propagule survival rate is reduced. The importance of high c_0 is rather obvious from equation (2). If all parasites are very successful in infecting a new host the probability of multiple infection no longer depends on propagule survival rate. The interaction between the mode of transmission and the impact of propagule survival is less intuitive. From equation (A1) (see Appendix A) it can be shown that, when some extinctions occur (i.e. $v^*>0$) and when $\phi=0$, relatedness is much less sensitive to variations in the cost of dispersal (and therefore to variations in propagule survival). However, this might be an artefact due to the assumption of very large fecundity. Indeed, if I assume that each parasite produces only a small number of offspring the effect shown in figure 2 (i.e. the increase of parasite virulence with higher propagule survival) is qualitatively similar when $\phi=0$ (not shown).

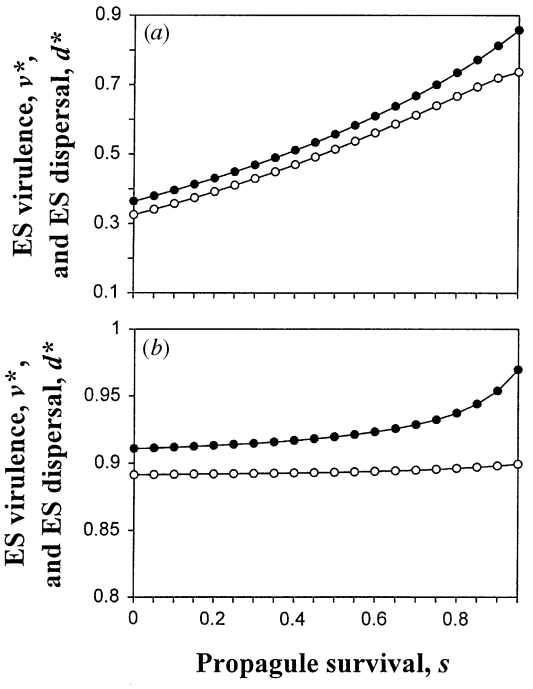

Figure 3. Coevolution of virulence with dispersal. Evolutionarily stable level of virulence, v^* (in white), and of dispersal, d^* (in black), versus propagule survival rate when virulence and dispersal are unlinked traits. In (a) $\phi=1$ (probability of common origin), and in (b) $\phi=0$. Other parameter values: $N=10$, $c_0=0.9$.

(b) *Coevolution of virulence and dispersal*

Parasite dispersal rate is also likely to evolve. Gandon & Michalakis (1999) have recently derived an analytic expression for the ES dispersal rate:

$$d^* = \frac{A - \sqrt{(A^2 - 4e(1-R\phi)B)}}{2B}, \qquad (20)$$

where

$$A = c + e^2(1-c) + e - R(1-e) - 2e\phi R(c + e(1-c)),$$

$$B = (c + e(1-c))^2 - R(1-e) - \phi R((1-c)^2 - e(3 - 6c + 2c^2) + e^2(3 - 4c + c^2)).$$

This expression generalizes the formulae for the ES dispersal rate obtained in simpler models (Van Valen 1971; Hamilton & May 1977; Comins *et al.* 1980; Frank 1986; Taylor 1988). Because higher propagule survival decreases the cost of dispersal (see equation (2)), it generally selects for higher dispersal rates (see equation (20)). Therefore, higher survival selects independently for both higher virulence (see figure 2) and higher dispersal.

More interestingly, with expressions (19), (20) and (A1) (see Appendix A) it is now possible to study the coevolution of parasite dispersal and parasite virulence as a function of propagule survival. Not surprisingly, figure 3 shows that, when $\phi=1$, both virulence and dispersal increase with higher propagule survival. However, note that the rate of increase of the ES virulence with propagule survival tends to be higher when parasite dispersal is also evolving (compare figures 2 and 3*a*). This can be

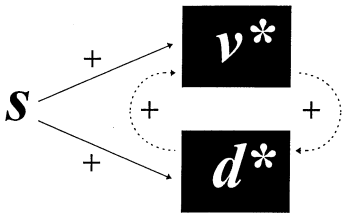

Figure 4. Schematic representation of the effects of higher propagule survival, s, on the evolutionarily stable virulence, v^*, and dispersal, d^*, when both traits are coevolving. Higher propagule survival selects independently for higher (+) virulence and higher dispersal (arrows) and these effects are strengthened by synergistic effects between virulence and dispersal (dashed arrows).

explained by a synergistic effect that emerges from the coevolution between dispersal and virulence (figure 4). First, higher dispersal selects for higher virulence (see figure 2) and, second, higher virulence selects for higher dispersal because higher virulence increases the extinction rate, e, of parasite populations.

Lower values of ϕ decrease relatedness (see equation (A1) in Appendix A), select for higher dispersal rates (see equation (20)) and, as a consequence, select for higher virulence (compare figure 3*a* and 3*b*). As in the previous case (when dispersal does not evolve), propagule survival does not affect the evolution of virulence when ϕ and c_0 are small.

5. LINKING VIRULENCE AND DISPERSAL

In the previous section, I studied the evolution of virulence when dispersal and virulence are not linked. Let me now assume that dispersal and virulence are correlated traits. Depending on the biology of a given host–parasite interaction it might be relevant to consider either positive or negative correlations between dispersal and virulence. For example, high virulence of myxoma virus is typically associated with lots of open skin lesions. In this case the vector (fleas or mosquitoes) can more easily bite infected wounds and transmit the virus (Anderson & May 1982). As a consequence, higher transmission ability is associated with higher virulence. Alternatively, dispersal may be associated with lower virulence. For example, Ebert & Mangin (1997) recently suggested that there could be a negative correlation between within-host growth rate (i.e. virulence) and dispersal of a horizontally transmitted microsporidian parasite of *Daphnia magna*. Such a trade-off might also be very likely in predator–prey systems in which it has been shown that an increase in predator dispersal rate might decrease predation load (Diekmann *et al*. 1988; Jansen & Sabelis 1992; van Baalen & Sabelis 1995*b*). As pointed out by van Baalen & Sabelis (1995*b*), there are strong analogies between the evolution of parasite virulence and the evolution of predation rate. One can track both questions using the general kin-selection model presented in this paper.

In the following, I will only consider two extreme and opposite subcases. First, dispersal is positively correlated with virulence ($d=v$) and, second, dispersal is negatively correlated with virulence ($d=1-v$). In both situations, dispersal and virulence will be considered to be expressions of a single pleiotropic trait (Frank 1994). I will use the general expression of parasite fitness (equation (12)) to derive the ESSs. Unfortunately, it was not possible to derive simple analytic expressions of the ESSs. In the following, I will present numerical solutions of the ESSs for the two extreme subcases.

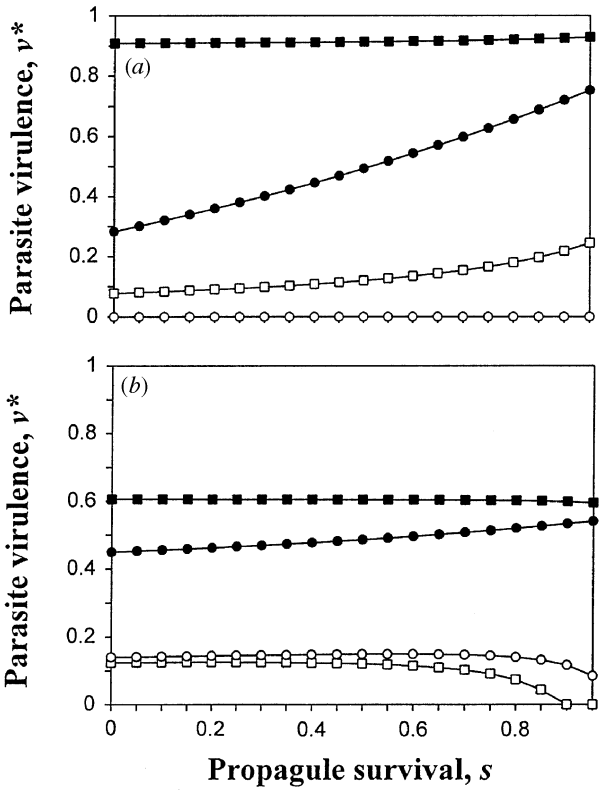

Figure 5. Evolutionarily stable level of virulence, v^*, versus propagule survival, s, for two different probabilities of common origin ($\phi=0$ (squares) and $\phi=1$ (circles)), and for two population sizes ($N=1$ (white) and $N=10$ (black)), when virulence and dispersal are linked traits. In (*a*) virulence and dispersal are positively correlated ($v^*=d^*$), and in (*b*) virulence and dispersal are negatively correlated ($v^*=1-d^*$). Other parameter value: $c_0=0.9$.

(a) *Positive correlation*

As in the previous case (i.e. when dispersal and virulence are unlinked), larger population sizes and lower probability of common origin select for higher levels of parasite virulence (figure 5*a*). Moreover, figure 5*a* shows that higher propagule survival generally selects for higher virulence. This is not surprising as we saw that dispersal and virulence are both selected for when propagule survival increases (see figures 3 and 4). The point I would like to raise here is that, in this situation, there are multiple causes for the increase of virulence with propagule survival. First, propagule survival may act indirectly through its effect on the probability of multiple infection and, ultimately, on the level of relatedness among parasites (see figure 3). Second, propagule survival may act directly on virulence (through its effect on the evolution of dispersal), because higher survival decreases the cost of dispersal. Depending on the parameter values, one of these effects can be preponderant. For example, when $N=1$ there is no indirect effect as $R=1$. In this case, the

increase of virulence with higher propagule survival (see figure 5*a* when $\phi=0$ and $N=1$) is only due to selection for higher dispersal rates. Because dispersal and virulence are positively correlated, both direct and indirect effects affect the evolution of parasite virulence in the same way. This is no longer the case if there is a negative correlation between virulence and dispersal.

(b) *Negative correlation*

Again, larger population sizes select for higher parasite virulence (figure 5*b*). Concerning the effects of the other parameters (ϕ, s) there are strong interactions. As in the previous case, propagule survival can act either indirectly or directly.

When $N=10$, indirect effects can occur. In this situation, figure 5*b* shows that high propagule survival selects for high virulence when $\phi=1$. When $\phi=0$ there is almost no effect of parasite survival rate. When $N=1$, the relatedness among parasites does not depend on propagule survival as $R=1$. In this situation, only direct effects via the evolution of dispersal may affect the evolution of virulence. In this case, higher propagule survival always selects for higher dispersal and, because of the negative correlation, for lower level of parasite virulence (whatever the value of ϕ). This result illustrates the fact that direct and indirect effects may act in different directions. Indirect effects select for higher virulence but direct effects, via selection on dispersal, select for lower level of parasite virulence. The evolutionary outcome results from a balance between these opposing forces.

6. DISCUSSION

(a) *The curse of the pharaoh*

In this paper, I investigate the validity of the curse of the pharaoh hypothesis or, in other words, whether propagule survival can affect the evolution of parasite virulence. Bonhoeffer *et al.* (1996) formally analysed this hypothesis when only single infections occur. They showed that when the host–parasite system has reached an ecological equilibrium, the ES parasite virulence does not depend on propagule survival. However, in some non-equilibrium situations, they found that the ES virulence is indeed an increasing function of propagule survival. In this paper, following the investigation of Bonhoeffer *et al.*, I present a general kin-selection model (modified from Frank (1994)) that allows me to incorporate the effects of multiple infections and of the evolution of parasite dispersal. In this case, contrary to Bonhoeffer *et al.* (1996), I found that, at ecological equilibrium, higher propagule survival generally increases parasite virulence. However, different subcases have to be considered depending on the correlation between virulence and dispersal.

First, when virulence and dispersal are unlinked, higher propagule survival always increases parasite virulence if there is (i) some basic cost of dispersal, and (ii) multiple infections. The first assumption is likely to be relevant in natural populations. For example, when the density of susceptible hosts is low it might be very difficult to find a susceptible host. The occurrence of multiple infections is also very likely for several microparasites species. Moreover, I showed that the effect of higher propagule survival is enhanced when parasite dispersal coevolves with parasite virulence because of synergistic effects (see figure 4). The ability for both parasite virulence and parasite dispersal to evolve has been recently demonstrated experimentally by Ebert & Mangin (1997). They followed the evolution of a microsporidian parasite *Glucoides intestinalis* of *Daphnia magna* and manipulated the extrinsic host mortality rate. After 14 months they showed that such experimental evolution affected both the evolution of parasite virulence and dispersal.

Second, when dispersal and virulence are correlated traits, propagule survival can affect the evolution of virulence through the evolution of dispersal. The correlation is likely to be positive for many parasite species and, in this case, virulence always increases with higher propagule survival. However, the correlation between virulence and dispersal may also be negative for some particular parasitic or predatory species. In this case, the qualitative effect of higher propagule survival may be altered by the interaction with other parameters (see figure 5*b*).

Recently, Walther & Ewald (1998) showed that, in accordance with the curse of the pharaoh hypothesis, there is a positive correlation between pathogen durability and mortality per infection in human respiratory pathogens (however, see Bonhoeffer *et al.* (1996) for contrasting examples). It might be interesting to analyse which of the different alternative explanations listed in the present paper (i.e. epidemic, multiple infection, positive correlation between virulence and dispersal) may explain the effect observed by Walther & Ewald (1998).

(b) *Inclusive effects and virulence management*

The modified version of the model of Frank (1994) which I present in this paper identifies two different forms of selective pressures. First, propagule survival can act directly on the evolution of virulence if dispersal and virulence are correlated traits. Second, propagule survival can also act indirectly if one takes into account its impact on the relatedness among parasites within an infected host. In certain cases, direct and indirect effects may act in different directions (e.g. when there is a negative correlation between virulence and dispersal). This work indicates the relevance of studying the inclusive effects (i.e. the combination of direct and indirect effects) of higher propagule survival when the host–parasite system has reached an ecological equilibrium. However, the study of the inclusive effects in non-equilibrium conditions remains to be carried out.

This study further shows that several other parameters that affect the transmission of parasites may also act indirectly on the evolution of parasite virulence. For example, the mode of dispersal (i.e. the probability of common origin, ϕ) affects greatly the ES parasite virulence. Higher probability of common origin tends to decrease virulence. Moreover, the likelihood of being transmitted may also affect virulence. Higher costs of dispersal tend to decrease parasite virulence. This result may be useful in clarifying another hypothesis. Ewald (1991, 1993, 1994) proposed that higher contact rate in sexually transmitted diseases like AIDS should promote

the evolution toward higher parasite virulence. The direct effects of such a parameter have been studied by Lipsitch & Nowak (1995; see also Massad 1996; Lipsitch 1997), but the extrapolation of the present paper suggests that the indirect effects of contact rate could affect the evolutionary outcome through within-host evolution. There are several subcases to consider. If only single infections occur, higher contact rates may select for higher virulence only in some non-equilibrium situations (Lipsitch & Nowak 1995). If the host–parasite system has reach an epidemiological equilibrium, this effect (i.e. the increase of parasite virulence with contact rate) may hold only if multiple infections occur.

These results have practical implications since a better understanding of the parameters that affect virulence may lead to particular strategies for public health. For example, as suggested by Ewald (1993, 1994), improved sanitation could decrease parasite propagule survival rate and, as a consequence, decrease parasite virulence. In a more general way, a decrease in parasite transmission ability may have two types of beneficial effects on public health. First, at the individual host scale, lower parasite transmissibility may lower the probability of being infected. Second, in the long term, such interventions may, under certain conditions, select for lower parasite virulence and, as a consequence, benefit the entire host population.

I thank Y. Michalakis, O. Ronce, G. Sorci and M. van Baalen for comments and clarifications.

APPENDIX A

Very generally, relatedness, R, can be written in the following way (Taylor & Frank 1996):

$$R = \frac{\mathrm{cov}(H_y, G_x)}{\mathrm{cov}(H_x, G_x)},$$

where G_x is the genotypic value of an individual x, and H_x and H_y are the phenotypic values of x and of a random patchmate, y, of x. If I further assume that selection is weak (which is very likely if phenotypic variations are very small) and that genes act additively, relatedness can be expressed as a function of coefficients of identity by descent (Michod & Hamilton 1980; Taylor 1988):

$$R = \frac{f_{xy}}{f_{xx}},$$

where f_{xy} is the coefficient of consanguinity between x and y (Crow & Kimura 1970); that is, the probability that random alleles from x and y are identical by descent. In what follows I will derive the coefficient of consanguinity of an individual x to a random patchmate y. Because I further assume haploidy and asexuality, $f_{xx}=1$ (an offspring has all the genes of its mother), R is equivalent to the coefficient of consanguinity, $f=f_{xy}$. Whitlock & McCauley (1990) developed an analytic formulation of this measure when extinctions occur. Using a similar recurrence equation I get

$$f_t = M_1 + M_2((1-m)^2 f_{t-1} + m^2\gamma),$$

where M_1 and M_2 are the probability that two individuals in the population are or are not sibs, respectively. When fecundity is very large:

$$M_1 = 1/N$$

$$M_2 = (N-1)/N.$$

The parameter m is the immigration rate and is equal to

$$m = \frac{(1-c)(1-e)d}{1-d+(1-c)(1-e)d}.$$

We assume that individual parasites taken from different infected hosts are not related and therefore immigrants may be related only if they have emigrated from the same host. γ is the probability of identity of two immigrants and is equal to

$$\gamma = \lim_{n\to\infty}(U_n),$$
$$U_n = \phi(M_1 + M_2((1-m)^2\hat{f} + m^2 U_{n-1})),$$
$$\gamma = \frac{\phi(M_1 + M_2((1-m)^2\hat{f}))}{1-\phi\, m^2\, M_2}.$$

where $\hat{f}$ is the average coefficient of consanguinity in the metapopulation. Then, for newly founded populations we have

$$f_0 = R_0 = M_1 + M_2\gamma.$$

At the scale of the metapopulation this leads to

$$R' = \sum_{t=0}^{\infty} F_t R_t = \sum_{t=0}^{\infty} F_t f_t = \hat{f},$$
$$R' = eR_0 + (1-e)\sum_{t=1}^{\infty}\{F_{t-1}[M_1 + M_2((1-m)^2 R_{t-1} + m^2\gamma)]\},$$
$$R' = eR_0 + (1-e)\left[M_1 + M_2((1-m)^2 R + m^2\gamma)\right].$$

At equilibrium we then have

$$R = \frac{e(M_1+\phi(1-m^2)(M_1M_2)) + (1-e)M_1}{1-\phi M_2(m^2+e(1-m)^2M_2) - (1-e)(1-m)^2M_2}. \quad \text{(A1)}$$

REFERENCES

Anderson, R. M. & May, R. M. 1979 Population biology of infectious diseases. I. *Nature* **280**, 361–367.

Anderson, R. M. & May, R. M. 1982 Coevolution of hosts and parasites. *Parasitology* **85**, 411–426.

Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control*. Oxford University Press.

Bonhoeffer, S., Lenski, R. & Ebert, D. 1996 The curse of the pharaoh: the evolution of virulence in pathogens with long living propagules. *Proc. R. Soc. Lond.* B **263**, 715–721.

Bremermann, H. J. & Pickering, J. 1983 A game-theoretical model of parasite virulence. *J. Theor. Biol.* **100**, 411–426.

Comins, H. N., Hamilton, W. D. & May, R. M. 1980 Evolutionarily stable dispersal strategies. *J. Theor. Biol.* **82**, 205–230.

Corelli, M. 1923 The curse of osiris. *Daily News*, 5th April, p. 1. London.

Crow, J. A. & Kimura, K. L. 1970 *An introduction to population genetics theory*. New York: Harper & Row.

Diekmann, O., Metz, J. A. & Sabelis, M. W. 1988 Mathematical model of predator/prey/plant interactions in a patch environment. *Expl Appl. Acarol.* **5**, 319–342.

Ebert, D. & Mangin, K. L. 1997 The influence of host demography on the evolution of virulence of a microsporidian gut parasite. *Evolution* **51**, 1828–1837.

Eshel, I. 1977 On the founder effect and the evolution of altruistic traits: an ecogenetical approach. *Theor. Popul. Biol.* **11**, 410–424.

Ewald, P. W. 1983 Host–parasite relations, vectors and the evolution of disease severity. *A. Rev. Ecol. Syst.* **14**, 465–485.

Ewald, P. W. 1987 Pathogen-induced cycling of outbreaks in insect populations. In *Insect outbreaks* (ed. P. A. Barbosa & J. C. Schultz), pp. 269–286. London: Academic Press.

Ewald, P. W. 1991 Transmission modes and the evolution of virulence, with special reference to cholera, influenza and AIDS. *Hum. Nat.* **2**, *1–30.*

Ewald, P. W. 1993 Evolution of virulence. *Scient. Am.* **268**, 86–93.

Ewald, P. W. 1994 *The evolution of infectious disease*. Oxford University Press.

Frank, S. A. 1986 Dispersal polymorphisms in subdivided populations. *J. Theor. Biol.* **122**, 303–309.

Frank, S. A. 1994 Kin selection and virulence in the evolution of protocells and parasites. *Proc. R. Soc. Lond.* B **258**, 153–161.

Frank, S. A. 1996 Models of parasite virulence. *Q. Rev. Biol.* **71**, 37–78.

Gandon, S. & Michalakis, Y. 1999 The evolution of dispersal in a metapopulation with extinctions and kin competition. (Submitted.)

Hamilton, W. D. 1964 The genetical evolution of social behaviour. *J. Theor. Biol.* **7**, 1–52.

Hamilton, W. D. & May, R. M. 1977 Dispersal in stable habitats. *Nature* **269**, 578–581.

Herre, E. A. 1993 Population structure and the evolution of virulence in nematode parasites of fig wasps. *Science* **259**, 1442–1446.

Jansen, V. A. A. & Sabelis, M. W. 1992 Prey dispersal and predator persistence. *Expl Appl. Acarol.* **14**, 215–231.

Lipsitch, M. 1997 Transmission rates and HIV virulence: comments to Massad. *Evolution* **51**, 319–320.

Lipsitch, M. & Nowak, M. A. 1995 The evolution of virulence in sexually transmitted HIV/AIDS. *J. Theor. Biol.* **174**, 427–440.

Massad, E. 1996 Transmission rates and the evolution of HIV virulence. *Evolution* **50**, 916–918.

May, R. M. & Nowak, M. A. 1995 Coinfection and the evolution of parasite virulence. *Proc. R. Soc. Lond.* B **261**, 209–215.

Michod, R. E. & Hamilton, W. D. 1980 Coefficient of relatedness in sociobiology. *Nature* **288**, 694–697.

Nowak, M. A. & May, R. M. 1994 Superinfection and the evolution of virulence. *Proc. R. Soc. Lond.* B **255**, 81–89.

Olivieri, I., Michalakis, Y. & Gouyon, P.-H. 1995 Metapopulation genetics and the evolution of dispersal. *Am. Nat.* **146**, 202–228.

Taylor, P. D. 1988 An inclusive model for dispersal of offspring. *J. Theor. Biol.* **130**, 363–378.

Taylor, P. D. & Frank, S. A. 1996 How to make a kin selection model? *J. Theor. Biol.* **180**, 27–37.

Taylor, L. H., Mackinnon, M. J. & Read, A. F. 1998 Virulence of mixed-clone and single-clone infections of the rodent malaria *Plasmodium chabaudi*. *Evolution*. (In the press.)

van Baalen, M. & Sabelis, M. W. 1995*a* The dynamics of multiple infection and the evolution of virulence. *Am. Nat.* **146**, 881–910.

van Baalen, M. & Sabelis, M. W. 1995*b* The milker-killer dilemma in spatially structured predator–prey interactions. *Oikos* **74**, 391–400.

van Valen, L. 1971 Group selection and the evolution of dispersal. *Evolution* **25**, 591–598.

Walther, B. A. & Ewald, P. W. 1998 Pathogen survival in the external environment and the evolution of virulence. *Q. Rev. Biol.* (In the press.)

Whitlock, M. C. & McCauley, D. E. 1990 Some population genetic consequences of colony formation and extinction: genetic correlations within founding groups. *Evolution* **44**, 1717–1724.

As this paper exceeds the maximum length normally permitted, the author has agreed to contribute to production costs.